

wherein

R^2 is as defined above; and

A 4 L is selected from the group consisting of hydroxy, halo, azido, mono-(C_{1-16} alkyl)carbonate, (C_{1-6} alkyl)carboxylate, (C_{6-10} aryl)carboxylate, mono-(C_{6-10} aryl)-(C_{1-6} alkyl)carboxylate, di-(C_{6-10} aryl)(C_{1-6} alkyl)carboxylate, di(C_{1-6} alkyl)phosphorothioate, (C_{1-6} alkyl)sulfonyl, mono-(C_{1-6} alkyl)(C_{6-10} aryl)sulfonyl, di-(C_{1-6} alkyl)-(CO)-S-, cyano- C_{1-6} alkoxy, C_{6-10} aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl; in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.

REMARKS

All the claims submitted for examination in this application have been rejected on formal and/or substantive grounds. Applicants have amended the specification and claims and respectfully submit that all the claims currently in this application are patentable over the rejections of record.

Turning first to the formal ground of rejection, Claims 1-5 and 7-20 stand rejected, under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the C_{3-10} cycloalkyl meaning of A^2 in Claim 1 is deemed defective. This is so insofar as the specification, at Page 5, line 12, refers to one or two optional double bonds in its definition. That meaning, the Official Action avers, would define cycloalkenyl.

Applicants respectfully submit that the meaning of "cycloalkyl," as defined in the specification at Page 5, lines 9-15, encompass a meaning of C_{3-10} cycloalkenyl. Attention is

again directed to the portion of the specification at Page 5, lines 9-15. Therein the term “cycloalkyl” includes within its meanings cyclopentenyl and cyclohexenyl. These two radicals are representative of the class of cycloalkenyls within the contemplation of the term “cycloalkyl.”

Applicants submit that it is axiomatic that applicants are their own lexicographers Oakley, Inc. v. Sunglass Hut Intern., 316 F.3d 1331 (Fed Cir 2003). Although applicants concede that the terms “cycloalkyls” and “cycloalkenyls” are oftentimes used independently, the use of the former term to encompass the latter term is not contrary to a proper understanding, by those skilled in the art, of the invention of the present application.

However, applicants admit it might be preferable to use both of these meanings of A² in the specification and claims of the present application. Therefore, applicants have amended the specification to clarify this matter. The meaning of A² has been extended to encompass “C₃₋₁₀ cycloalkenyl.” Moreover, the aforementioned meanings of A², cyclopentenyl and cyclohexenyl, have been deleted from the paragraph of the specification beginning at Page 5, line 9.

A new paragraph, beginning after line 15 of Page 5 of the specification, has been added to define meanings of cycloalkenyl within the scope of A². These meanings include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and cyclononenyl. Support for this additional material is provided in the originally filed specification at Page 5, lines 12-13. Therein it is recited that the term “cycloalkyl” means, in addition to saturated cycloalkyls, those containing one double bond. Insofar as cycloalkyl is defined as C₃₋₁₀ and that meaning includes cycloalkyls containing one double bond, each of the aforementioned meanings of cycloalkenyls having 3 to 10 carbon atoms are within the contemplation of the present

application and their introduction into the specification does not represent the inclusion of new matter.

In view of the aforementioned amendment to the specification, which is fully supported by originally filed specification and thus represents no new matter, the meaning of A² in Claim 1 has been amended to include C₃₋₁₀ cycloalkenyl. The above-discussed amendment to the specification provides the specification with the requisite support for this amendment to the claims.

All the claims currently in this application have been rejected on two related substantive grounds. The first substantive ground of rejection is directed to Claims 1-11, 13-16 and 20-24. These claims stand rejected, under 35 U.S.C. 103(a), as being unpatentable over International Publication No. WO 92/01696 to Bateson et al.

The basis for this ground of rejection, as explained in the Official Action, is that the acylation process disclosed in Bateson et al. at Page 17, line 24 et seq. employs compound II, where n is 0 and where CO₂R³ can be carboxy or a salt thereof. The Official Action thus admits that the examples in Bateson et al. require acylation to occur solely in the presence of esters, e.g. Example 1, step g, Example 2, step h and Example 13, step g. The Official Action argues that this sole distinction between the claims of the present application and those of Bateson et al., that the claimed process of the present application limits the group CO₂R¹ to a carboxylic acid or salt thereof whereas the teaching of Bateson et al. is limited to carboxylic esters, is not enough to argue that the applied reference does not present a prima facie case of obviousness. Indeed, the Official Action states that the difference between the use of an acid in the claims of the present application and the use of an ester in the applied Bateson et al.

reference provides a prima facie case of obviousness that can only be rebutted by the showing of unexpected results obtained by using an acid rather than an ester.

Applicants meet the challenge thrown down in the outstanding Official Action by submitting that the use of the acid, or salt thereof, presents unexpected results rebutting any presumption of obviousness created by the Bateson et al. disclosure.

Applicants respectfully point out that the applied reference does not address the unexpected reactivity between compounds II and III, as set forth in Claim 1, from which the remaining claims ultimately depend. The process of the present application is unexpectedly superior to the process taught in Bateson et al. insofar as reactivity between compound II, which is limited to an acid or a salt thereof, and compound III, wherein the leaving group L has the meanings given therein, is far higher than that obtained when the compound II is an ester, as taught in Bateson et al.

Whereas the reaction of the ester of compound II in Bateson et al. and compound III requires cryogenic conditions to provide high selectivity, the reaction between the acid or salt thereof of compound II and compound III in the present application occurs with high selectivity without the necessity of maintaining the high cost cryogenic thermodynamic conditions required by the Bateson et al. process.

The zwitterions condition of the acid of compound II allows this reaction to be effected by simple pH adjustment. This eliminates the need for a costly coupling agent and the harsh cryogenic temperatures required when an ester is employed. In addition, the step prior to reaction between compound II and III permits the zwitterions of compound II to be crystallized without undue difficulty which, in turn, permits the purging of impurities that

impact the final quality of the product 3-cyclic-ether-substituted cephalosporin having the formula I.

A second substantive ground of rejection is, in effect, applied in the rejection of Claims 23 and 24. These claims stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Bateson et al. insofar as Example 6, step d, Example 7, step a, Example 9, step a, Example 14, step d and Example 15, step d all teach the utilization of the p-methoxybenzyl esters. The Official Action avers that Claims 23 and 24, in which compound V is limited to R³ being p-nitrobenzyl or allyl, is obvious over the otherwise identical ester of Bateson et al. where R³ is p-methoxybenzyl.

Applicants emphasize that the limitation of Claims 23 and 24 of the present application, wherein R³ in compound V has the meanings p-nitrobenzyl or allyl, is not only not disclosed in Bateson et al. but, in addition, produces unexpectedly improved results in the claimed process of the earlier claims over the compound employed in Bateson et al., wherein R³ is p-methoxybenzyl.

When compound V in Claims 23 and 24 is limited to a meaning of R³ being p-nitrobenzyl or allyl, compound II may be crystalline. Those skilled in the art are aware that crystalline compounds are of higher purity than the less crystalline compound defined by R³ being p-methoxybenzyl in Bateson et al.

Furthermore, in comparing compound V where R³ is p-nitrobenzyl group, as set forth in Claims 23 and 24 of the present application, with the p-methoxybenzyl containing compound employed in Bateson et al., it is immediately appreciated that the claimed p-nitrobenzyl group is much more easily removed with sodium dithionate under very mild conditions. On the other hand, the utilization of p-methoxybenzyl requires the use of

hydrogenation conditions to remove that group. Those skilled in the art appreciate that that p-methoxybenzyl group cannot be removed at all with sodium dithionate.

Novel compound V of Claims 23 and 24, has the unique characteristic of allowing its CO_2R^3 group to be removed under mild pH adjustment. This adjustment produces the corresponding zwitterions which are then crystallized without having to remove any heterogeneous palladium. Sodium dithionate deprotection, in the teaching of Bateson et al., requires the utilization of the expensive precious metal palladium to remove the benzyl protecting groups taught by Bateson et al. As such, any presumption of obviousness created by the teaching in Bateson et al. of a compound containing a p-methoxybenzyl group is rebutted.

Applicants submit that the above remarks address the grounds imposed in the rejection, on substantive grounds, of the claimed process and product of the present application. Reconsideration and removal of these grounds of rejection is therefore deemed appropriate. Such action is respectfully urged.

The above amendment and remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims,

Claims 1-24, is therefore respectfully solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Marvin Bressler", with a long, sweeping horizontal line extending to the right.

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APPENDIX

RENDITION SHOWING CHANGES MADE TO THE APPLICATION

IN THE SPECIFICATION:

Amendment of the paragraph beginning at Page 5, line 1:

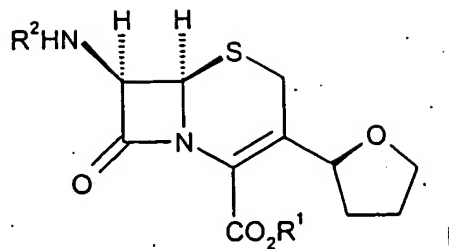
A² is hydrogen, C₁₋₆ alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkenyl, C₆₋₁₀aryl, C₁₋₆(CO)(C₁₋₆)alkyl-O-, HO(CO)C₁₋₆alkyl, mono-(C₆₋₁₀aryl)(C₁₋₆alkyl), di-(C₆₋₁₀)(C₁₋₆alkyl) or tri-(C₆₋₁₀aryl)(C₁₋₆alkyl); and R³ is para-nitrobenzyl or allyl, preferably allyl; with a suitable detecting agent in the presence of a solvent.

Amendment of the paragraph beginning at Page 5, line 9:

The term "cycloalkyl", as used herein, unless otherwise indicated, includes a mono or bicyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, [cyclopentenyl, cyclohexenyl,] bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally [containing 1 or 2 double bonds and optionally] substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C₁₋₄)alkoxy, (C₆₋₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁₋₄)alkyl, more preferably fluoro, chloro, methyl, ethyl [and] or methoxy.

IN THE CLAIMS:

1 (Amended): A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula I:

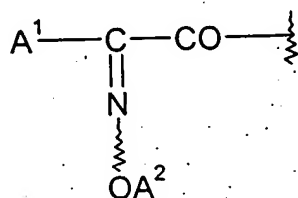


or a pharmaceutically acceptable salt thereof,

wherein

the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has the formula:

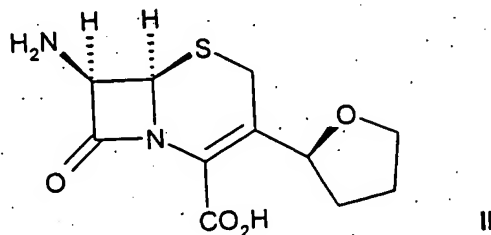


wherein

A^1 is selected from the group consisting of C_{6-10} aryl, C_{1-10} heteroaryl and C_{1-10} heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-16} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{6-10} aryl, C_{1-6} alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10} aryl)(C_{1-6} alkyl), di-(C_{6-10} aryl)(C_{1-6} alkyl), and tri-(C_{6-10} aryl)(C_{1-6} alkyl);

comprising reacting a compound formula II



with a compound of the formula III:

R^2L

III;

wherein

R^2 is as defined above; and

L is selected from the group consisting of hydroxy, halo, azido, mono-(C_{1-16} alkyl)carbonate, (C_{1-6} alkyl)carboxylate, (C_{6-10} aryl)carboxylate, mono-(C_{6-10} aryl)-(C_{1-6} alkyl)carboxylate, di-(C_{6-10} aryl)(C_{1-6} alkyl)carboxylate, di(C_{1-6} alkyl)phosphorothioate, (C_{1-6} alkyl)sulfonyl, mono-(C_{1-6} alkyl)(C_{6-10} aryl)sulfonyl, di-(C_{1-6} alkyl)-(CO)-S-, cyano- C_{1-6} alkoxy, C_{6-10} aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.